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**Endoscopic ultrasound in the diagnosis and management of carcinoma pancreas**

Puri R *et al*. EUS use for carcinoma pancreas

**Rajesh Puri, Manish Manrai,Ragesh Babu Thandassery, Abdulrahman A Alfadda**

**Rajesh Puri,** Institute of Digestive and Hepatobiliary Sciences, Medanta, The Medicity, Gurgaon 122001, Haryana, India

**Manish Manrai,**Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

**Ragesh Babu Thandassery,** Department of Medicine, Division of Gastroenterology, Hamad General Hospital, Doha 3050, Qatar

**Abdulrahman A Alfadda,** Department of Medicine, Division of Gastroenterology, King Faisal Specialist Hospital and Research Center, Riyadh 12713, Saudi Arabia

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**Correspondence to:** **Ragesh Babu Thandassery, MD, DM,** Department of Medicine, Division of Gastroenterology, Hamad General Hospital, 2 South 2, Doha 3050, Qatar. doc.ragesh@gmail.com

**Telephone:** +974-44-392532

**Fax:** +974-44-392279

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**Abstract**

Endoscopic ultrasound (EUS) has become an important component in the diagnosis and treatment of carcinoma pancreas. With the advent of advanced imaging techniques and tissue acquisition methods the role of EUS is becoming increasingly important. Small pancreatic tumors can be reliably diagnosed with EUS. EUS guided fine needle aspiration establishes diagnosis in some cases. EUS plays an important role in staging of carcinoma pancreas and in some important therapeutic methods that include celiac plexus neurolysis, EUS guided biliary drainage and drug delivery. In this review we attempt to review the role of EUS in diagnosis and management of carcinoma pancreas.

**Key words**: Carcinoma pancreas; Endoscopic ultrasound; Treatment

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**Core tip:** Endoscopic ultrasound (EUS) is becoming increasingly important in the diagnosis and management of carcinoma pancreas. It helps in identification of small tumors, histological diagnosis by fine needle aspiration, staging of the disease and its treatment. Palliation of pain with celiac plexus neurolysis and palliation of jaundice by biliary drainage can be achieved with EUS guided techniques. In this review we attempt to review the role of EUS in different aspects of diagnosis and treatment of carcinoma pancreas.

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**INTRODUCTION**

Pancreatic cancer, according to SEER database in the United States, constitutes 3% of all new cancer cases. The number of new cases of pancreas cancer was 12.4 per 100000 men and women per year and the number of deaths were 10.9 per 100000 men and women per year based on 2008-2012 cases. It is more common with increasing age and slightly more common in men than women. The median age of diagnosis was 71 years, the median age of death being 73 years. It is estimated that there will be 48960 new cases of pancreas cancer and an estimated 40560 people will die of this disease in 2015. Using statistical models for analysis, rates for new pancreas cancer cases have been rising on average 0.8% each year over the last 10 years but the death rates have been stable, the 5 year survival being a dismal 5%-7.2%[1,2]. This spells out the magnitude of the problem with this disease.

The role of endoscopic ultrasound (EUS) evaluation of pancreatic cancer was suggested as an independent predictor of survival and improvement in patients with loco regional pancreatic cancer in a recent study[3]. We will highlight the various aspects of the role of EUS in the setting of pancreatic cancer.

**EUS FEATURES OF NORMAL PANCREAS AND PANCREATIC MALIGNANCY**

Natterman *et al*[4] and Catalano *et al*[5] described the pancreatic parenchyma as a homogeneous fine granular, reticulated pancreas with smooth margins without evidence of side-branch ectasia. The pancreatic duct diameter in the body was 1.7 to 1.9 mm on average (range, 1-3 mm), a ventral anlage (echogenic difference between the ventral and dorsal pancreas) was seen in up to 68% of controls. These data from control populations and healthy volunteers provide important standards for the normal endosonographic appearance of the pancreas but are limited by their small numbers and potential biases in control populations.

On the other hand, neoplastic masses may obscure the normal parenchymal and ductal features. They are generally more homogeneous; hypoechoic compared to surrounding tissue and are rarely calcified. In a calcified pancreas, neoplastic lesions frequently push the calcified parenchyma towards the periphery. In addition signs of vascular invasion are highly suggestive of malignancy[6].

**DIAGNOSTIC ROLE OF EUS IN PANCREATIC CANCER**

EUS has high sensitivity for detecting pancreatic neoplasms and further provides the ability to obtain samples from suspected lesions by fine needle aspiration (FNA) contributing to its accuracy in the diagnosis of pancreatic cancer. It has been considered one of the most precise methods for the detection of pancreatic focal lesions, especially in patients with small tumors of 3 cm or less[7,8] (Figure 1). The reported sensitivity and accuracy of combined EUS-FNA for detecting pancreatic malignancy usually exceeds 90%[9-14]. A recent meta-analysis mentioned the pooled sensitivity and specificity of EUS FNA ranging between 87% and 96%, respectively, for diagnosing a solid pancreatic mass lesion[15]. The sensitivity and accuracy of EUS are slightly higher than the sensitivity and accuracy of computed tomography (CT) and Magnetic resonance imaging (MRI) in detecting small pancreatic lesions[16-19].

EUS can be used to assess TNM staging of pancreatic tumors. T1 lesions are smaller than 2 cm, T2 are lesions larger than 2 cm, tumor extending beyond the pancreas is either a T3 (portal vein, duodenum, or ampulla of Vater) or T4 lesions (extending to the celiac artery or superior mesenteric artery; being unresectable). Malignant nodes around the pancreas are N1 lesions and rarely distant metastasis may be seen (M1 lesion). The accuracy of CT, MRI, and EUS in assessing TNM staging of pancreatic cancer was compared by Soriano *et al*[20] wherein EUS had the highest accuracy for N-staging (65%) although CT was more accurate in assessing vascular invasion and T- staging. However in a retrospective study from Russia by Egorov *et al*[21], arterial encasement on CT did not necessarily indicate arterial invasion and in unresectable pancreatic cancers (on CT), EUS data for peripancreaticarterial involvement might suggest possible radical resection, providing survival benefits. It has also been used as a screening tool for individuals at a high risk for pancreatic cancer with incidence of clinically relevant findings at first screening being 7% with asymptomatic cancer and 16% premalignant IPMN-like lesions in a study by Poley *et al*[22].

The diagnostic reliability of EUS-FNA in the evaluation of pancreatic lesions is predictably affected by operator expertise, cytopathologic interpretation, and other variables including the presence of inflammatory changes[9,23]. A definite diagnosis cannot be ascertained in a significant minority of EUS-FNA samples alone, resulting in a cytological diagnosis of suspicious or indeterminate for neoplasm which is seen in approximately 8% to 10% of EUS-FNA samples, representing a challenging diagnostic dilemma[12,23,24]. In addition, presence of chronic pancreatitis may decrease the sensitivity of EUS-FNA as noted by Varadarajulu *et al*[25] where in the sensitivity was ranging from 73% to 91%, being lower in patients with chronic pancreatitis; and the No Endosonographic Detection of Tumor (NEST) study[26] had revealed 60% patients with co-existing chronic pancreatitis and 15% patients with a diffuse malignancy which was not detected earlier. Furthermore Siddiqui et al in their retrospective cohort trial found a false positive rate for EUS-FNA of solid pancreatic lesions of 1.1% as a result of cytologic misinterpretation in the setting of chronic pancreatitis[27].

Few basic remedial factors to improve the yield of EUS FNA were the use of 25 gauge needle as less blood is aspirated instead of conventional 22 gauge needle[28-30], combining cytologic and histologic analyses of the specimen to decrease the number of passes to 2[31] from 4 to 7 passes[32] (higher in pancreatic cancer than in other lesions), to cater for rapid on-site cytological evaluation[33-35], the use of serum CA19-9[36] and fluid CEA and CA19-9 for increasing the ability to diagnose malignancy especially in suspicious cases[37].

**WHAT IS NEW FOR DETECTION OF PANCREATIC MALIGNANCY?**

Developments have taken place to further refine the ability to differentiate a malignant lesion from a benign one with a reasonable certainty and overcome other limitations. There have been improvements in the imaging techniques with EUS as well as advances in cytopathology analysis. Among the newer technologies there are EUS elastography, contrast enhanced EUS and use of chromosomal detection techniques in FNA specimen.

EUS elastography is a noninvasive technique that measures elasticity in real time by registration of differences in distortion of the EUS image after application of slight pressure by the EUS probe (Figures 2 and 3). Tissue elasticity may be altered by inflammation, fibrosis and cancer resulting in distinct elastographic appearance. Initial studies were based on qualitative elastography evaluation, using a hue-color scale representing different degrees of tissue elasticity. Giovannini *et al*[38] had sensitivity and a specificity of 100% and 67% respectively while analyzing pancreatic masses using a scoring system based on different color patterns to differentiate between benign and malignant pancreatic masses. In asubsequent multicenter study[39], the sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic lesions were 92% and 80.0%, respectively, compared to 92% and 69%, respectively, for the conventional B-mode images. In another paper by Iglesias-García *et al*[40], malignancy could be diagnosed by qualitative EUS-elastography using color patterns with a sensitivity, specificity and overall accuracy of 100%, 85.5% and 94%, respectively. Recently quantitative EUS elastography has been developed in an attempt to make the elastography interpretation less subjective. Quantitative elastography gives a numeric result, either as mean value of hues in a selected area (mean hue histogram) or as a ratio of elasticity in the target area over soft reference tissue (strain ratio). Iglesias-García *et al[*41], have evaluated strain ratio in 86 consecutive patients with solid pancreatic masses and found the strain ratio was significantly higher among patients with malignant pancreatic tumors compared to those with inflammatory masses (Normal pancreatic tissue: 1.68, inflammatory masses: 3.28; pancreatic adenocarcinoma: 18.12; and the highest strain ratio was found among endocrine tumors). The sensitivity and specificity of the strain ratio for detecting pancreatic malignancies using a cutoff value of 6.04 were 100% and 92.9%, respectively, exceeding the accuracy obtained with qualitative elastography. Saftoiu *et al*[42] evaluated the usefulness of the hue-histograms in a multicenter study wherein a sensitivity of 93.4%, a specificity of 66.0%, a positive predictive value of 92.5% and an overall accuracy of 85.4% for the mean hue-histogram in the detection of malignancy were observed. In a further development, Schrader *et al*[43] had 100% sensitivity and specificity in differentiating benign from malignant lesions in tissues with blue color (hard tissue), on histogram with less discrimination on evaluating areas with red or green colors representing softer tissue. The role of this modality is still evolving to reduce the various biases of calculation of strain.

Contrast-enhanced (CE)-EUS consists of administration of contrast agents through the blood stream. The contrast agent contains microbubbles that can be detected by EUS in the small, low-velocity vasculature of pancreatic tumors on real-time evaluation. Initial studies using Levovist®, Albunex and FS 069 Optison as contrast agents demonstrated that the hyper vascular aspect of neuroendocrine tumors and the hypo vascular aspect of pancreatic adenocarcinoma[44-48]. Modern contrast enhanced EUS relies on a dedicated contrast harmonic echo-EUS (CHE-EUS) technique that detects signals from micro bubbles delivered by new contrast agents like Sonovue® in vessels with very slow flow as they have longer perfusion time and stronger backscatter without the burden of Doppler-related artifacts. Fusaroli *et al*[49] investigated 90 patients with solid pancreatic lesions by CEH-EUS, using Sonovue® as contrast agent. The finding of a hypo-enhancing mass with an inhomogeneous pattern diagnosed pancreatic adenocarcinoma with a sensitivity of 96% and an accuracy of 82%. The study also indicated that this CEH-EUS pattern diagnosed malignancy more accurately than the finding of a hypoechoic mass on standard EUS. Hyper-enhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). In a study by Napoleon *et al*[50], the finding of a hypo-enhanced lesion was able to detect malignancy with a sensitivity, specificity and accuracy of 89%, 88%, and 88.5%, respectively. Seicean *et al*[51] investigated the possibility to use quantitative CEH-EUS data in the differential diagnosis between pancreatic cancer and chronic pancreatitis. Ahypo-enhanced pattern was the most common finding both in pancreatic adenocarcinoma and in mass forming chronic pancreatitis. However, an index of contrast uptake ratio was calculated and this was significantly lower in adenocarcinoma compared to cases with mass-forming chronic with a sensitivity of 80% and a specificity of 91.7%. A recent prospective study by Kitano *et al*[52] showed that when CH-EUS was combined with EUS-FNA, the sensitivity of EUS-FNA increased from 92.2% to 100%. Data from South Korea showed a sensitivity and diagnostic accuracy of 93% and 92%, respectively for the diagnosis of pancreatic cancer[53]. In a recent retrospective study by Park *et al*[54] pancreatic adenocarcinomas showed a hypoenhanced pattern on CH-EUS with a sensitivity of 92%, the specificity of 68% and the accuracy approximately 82%.

In a recent review, Kitano *et al*[55] have mentioned that CH-EUS identifies pancreatic adenocarcinomas as solid lesions exhibiting hypo-enhancement with a sensitivity and specificity of 88%-96% and 88%-94%, respectively. In particular, 80%-100% of false-negative cases in EUS-FNA are correctly classified by CH-EUS, suggesting its complementary role. In addition, it improves depiction of some subtle lesions in conventional EUS, thus facilitating EUS-FNA. For quantitative perfusion analysis, a time-intensity curve (TIC) for the region of interest can be generated during CH-EUS. The maximum intensity gain and the echo intensity reduction rate from the peak at 1 min obtained by TIC can be used for differentiation of pancreatic adenocarcinoma from other tumors. CH-EUS is also useful for differentiation of invasive intraductal papillary mucinous neoplasms (IPMN) from non-invasive IPMN[55]. Thus, CH-EUS technology is very promising and is likely to play a role in the precise diagnosis of malignant pancreatic lesions.

The detection of various chromosomal abnormalities in FNA aspirates is a field which is rapidly evolving. It is useful in cases with indeterminate results and might help in confirming the diagnosis of a malignancy. Among the earlier studies, telomerase activity was studied by Mishra *et al*[56] which on combination with cytology results increased the sensitivity from 85% to 98% with 100% specificity. The use of fluorescence *in situ* hybridization (FISH) analysis by Kubiliun *et al*[57] on FNA specimens with inconclusive results revealed a sensitivity of 74% for detecting pancreatic cancer which increased to 85% on combining with cytology. Reicher *et al*[58] from US demonstrated the use of detecting K-ras mutation in addition to FISH analysis in precisely identifying 60% of atypical FNAs with final malignant diagnosis yielding 88% sensitivity and 94% specificity with 90% accuracy. The pooled sensitivity of EUS-FNA for the differential diagnosis of pancreatic adenocarcinoma was 80.6%, specificity was 97% and probable sensitivity and specificity were 76.8% and 93.3% for K-ras gene analysis, respectively. For combined EUS-FNA plus K-ras mutation analysis it was 88.7% and 92%, in a meta-analysis by Fuccio *et al*[59]. Overall, K-ras mutation testing applied to inconclusive cases by EUS-FNA reduced the false-negative rate by 55.6% albeit with a false-positive rate of 10.7%. Layfield *et al*[60] in their guidelines mention that many gene mutations (KRAS, GNAS, VHL, RNF43, and CTNNB1) may be of aid in the diagnosis of cystic neoplasms. The shortcoming of detecting chromosomal abnormalities in FNA specimens is that pancreatic cancers may express multiple mutations, detecting more might increase the sensitivity but with doubtful cost effectiveness.

**ROLE OF EUS IN THERAPEUTICS OF PANCREATIC CANCER**

The increasing use of EUS as a diagnostic modality has also led to its importance as an interventional tool in the management of pancreatic cancer. It ranges from assisting in radiotherapy, delivery of chemotherapeutic agents to palliation by celiac plexus neurolysis and biliary drainage wherever ERCP fails.

EUS delivery of antitumor agents is largely investigational and is still in experimental stage. The requirement to develop this option is due to pancreatic carcinoma having a poor response to chemo­therapeutic agents and radiation; and neoadjuvant chemotherapy can lead to a desmoplastic reaction further impairing drug delivery. Chang *et al*[61] used cytoimplant (Allogenic mixed lymphocyte culture) advanced pancreatic cancer with partial response noted in two patients. TNFerade biologic is a replication-deficient adenoviral vector that expresses tumor necrosis factor-α (TNF-α), regulated by a radiation inducible promoter; inducible by chemotherapy and radiation has been used by various authors. Hecht *et al*[62] had shown one complete response, 3 partial responses, and 12 patients with stable disease, overall 3 survived > 24 mo. Subsequently Hermen *et al*[63], reported in the randomized phase III trial among patients with locally advanced pancreatic cancer (LAPC) that though it is safe in combination with chemotherapy, it does not increase survival. ONYX-015, an adenovirus which preferentially replicates and kills malignant cells was studied by Hecht *et al*[64] wherein 2 patients had partial regression of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease with 2 patients each having sepsis and duodenal perforation. The injection of immature dendritic cells, which induce T-cell immune response against malignant cells, was used by Irisawa *et al*[65] successfully into the tumors of 7 patients with unresectable pancreatic cancer, with a cohort median survival of 9.9 mo. Thereafter, Hirooka *et al*[66] using the same therapy demonstrated effective responses in three of five patients; 1 had partial remission and 2 had long stable disease of more than 6 mo. This combined therapy was synergistically effective. Despite these studies, much more large prospective studies are required before these techniques are translated into clinical practice.

EUS guided brachytherapy has been carried out with radioactive seeds being placed into the tumour with the help of linear echoendoscope. The most popular radioactive seeds are Iodine 125, palladium 103 and iridium 192; iodine being the preferred radioactive material due to its long half life of 60 d in pancreatic cancers with rapidly dividing cells. Zin *et al*[67] in their experience achieved partial remission in three cases, estimated median survival time of nine months with improvement in pain but no survival benefit.

EUS guided fiducial insertion is being done in pancreatic malignancy to place markers inside the tumor for guiding stereotactic body radiotherapy. These markers can be radioactive spheres, coils or seeds. Its feasibility was shown by Pishvaian *et al*[68] wherein he reported a technical success of 85%. Subsequently in a prospective study by Park *et al*[69] fiducial insertion was successful in 88% of the 57 patients, Sanders *et al*[70] had a success rate of 90% for EUS fiducial insertion in a prospective study of 51 patients while DiMaio *et al*[71] achieved a success rate of 97% with a 22-gauge needle. Law *et al*[72] found this technique safe and feasible to assist intraoperative localization of small pancreatic neuroendocrine tumors. The 2 types of fiducials were compared by Khashab *et al*[73] in 39 patients with advanced pancreatic cancer. Traditional fiducials of 5 mm length had better visibility scores with similar migration rates as compared to viscoil fiducials of 10 mm length.

EUS-guided cryothermal ablation has been studied by Arcidiacono *et al*[74] in 22 patients with unresectable stage III pancreatic adenocarcinoma with a feasibility of 73% with insignificant tumor size reduction. Further studies are required to demonstrate progression-free survival and local effects. Recently Pai *et al*[75] used radiofrequency ablation (RF) which was applied with a monopolar RF probe (1.2 mm Habib EUS-RFA catheter) placed through a 19 or 22 gauge FNA needle after FNA was performed in patients with a tumor in the head of the pancreas with a 100% success rate. The response ranged from complete resolution to a 50% reduction in size. Oh *et al*[76,77] used EUS-guided ethanol lavage with paclitaxel injection (EUS-EP) for cystic tumors of the pancreas in two studies and found a 62%-99% resolution rate with adequate safety and feasibility. These data indicate the need for further large prospective studies to ascertain their roles in the management of pancreatic cancer.

EUS guided celiac plexus neurolysis (CPN)provides pain relief, palliation and reduces narcotic use in patients with unresectable pancreatic cancer[78]. The injection of a neurolytic drug into the celiac plexus disrupts the signal transmission to spinal cord and central nervous system. Due to the anatomical location of the celiac plexus around the origin of the celiac trunk and the superior-mesenteric artery, EUS- CPN provides real-time visualization for a safe approach.

EUS-CPN was demonstrated to be safe and effective in alleviating refractory pain due to pancreatic cancer in a meta-analysis of 8 studies by Puli *et al*[79]. Alcohol-based EUS-CPN was found safe and effective in this setting providing pain relief to 73% patients[80]. A recent RCT by Wyse *et al*[81] in 96 patients demonstrated greater pain relief in the early EUS-CPN group at three months than in conventional management group. As compared to opioids, EUS-CPN reduced pain at four and eight weeks and significantly reduced opioid consumption[82]. In addition a single central injection was found to be as effective as bilateral or multiple injections[83,84]. In another comparison between EUS-CPN and EUS-celiac ganglia neurolysis (CGN), Doi *et al*[85]observed higher treatment response rate and complete response rate in the EUS-CGN group compared to the EUS-CPN group.

EUS guided biliary drainage is another important area where therapeutic EUS is helpful. With failed ERCP biliary drainage can be established by 3 endoscopic methods (1, transluminal biliary drainage with hepaticogastrostomy or choledochoduodenomstomy, 2, EUS antegrade drainage and 3, EUS rendezvous drainage) [86].In 7% to 13% of patients with pancreatic head malignancy have duodenal stenosis, making ERCP technically challenging or impossible[87].

The role EUS guided biliary drainage in pancreatic cancer in failed ERCP has been recently demonstrated by Weilert[88] in 21 patients, 52% patients with pancreatic cancer wherein he achieved technical success in 20/21 (95.2%) and clinical success 19/21 (90.4%). He noted that EUS-guided anterograde biliary drainage using the intra-hepatic access route had high technical and clinical success with low adverse rate. In a recent study of 208 patients with malignant distal CBD obstruction requiring SEMS placement, authors compared the short-term outcome of single session EUS guided biliary drainage with ERCP[89].SEMS placement was successful in 97 and 98 patients in the respective groups (93.26% *vs* 94.23%, *P* = 1.00). The incidence of pancreatitis was higher with ERCP, and EUS group had superior treatment success rates in patients with duodenal stenosis.

**CONCLUSION**

EUS is rapidly becoming a sensitive and specific modality for diagnosing pancreatic cancer especially on combining with EUS-FNA albeit with difficulty in the presence of chronic pancreatitis. With the advent of newer technology in the form of EUS elastography, CE-EUS, and gene mutations detection in FNA specimens the diagnostic dilemma is better resolved. The availability of interventional EUS has allowed gastroenterologists to make significant difference in management of pancreatic cancer by its various therapeutic options including areas which have been traditionally dealt by surgeons and interventional radiologists. It is likely to become an important modality in the multidisciplinary management of pancreatic cancer.

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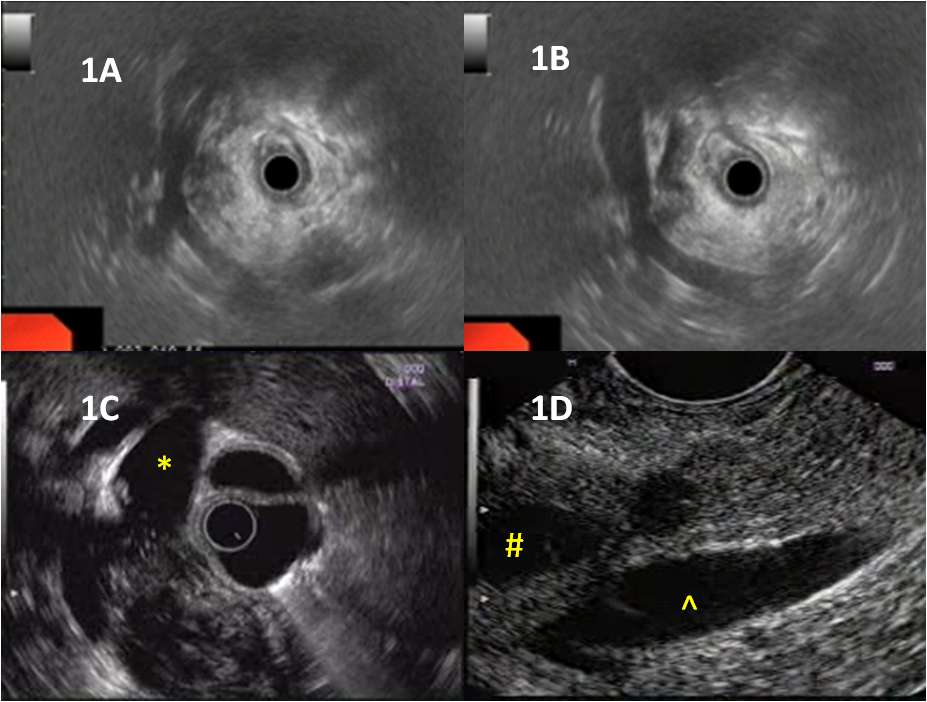
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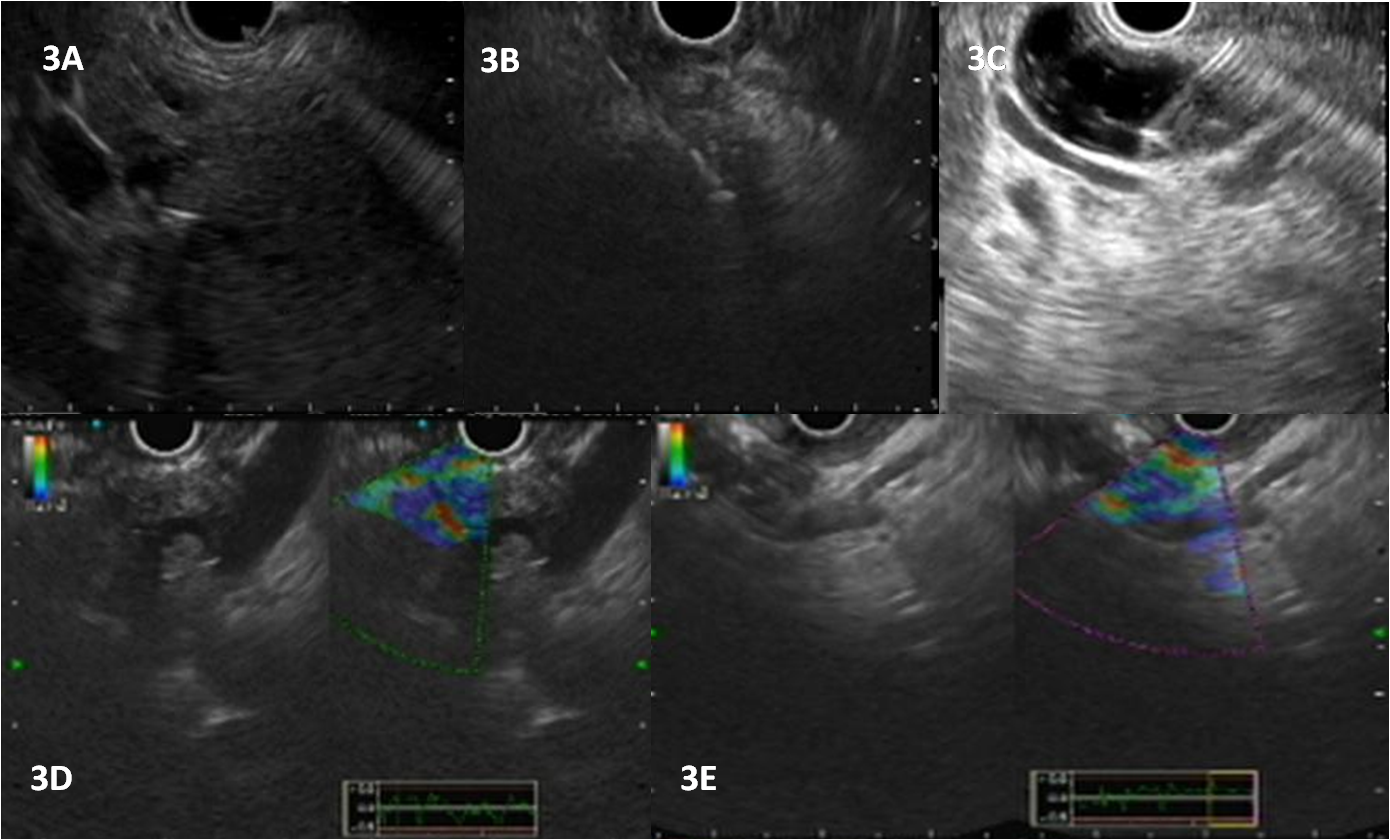
**P- Reviewer:** Klinge U, Yoshida H **S- Editor:** Song XX **L- Editor:** **E- Editor:**



**Figure 1 Endoscopic ultrasound appearance of mass lesions in pancreas.** A: Carcinoma head of pancreas with loss of fat planes with portal vein (PV); B: Carcinoma head of pancreas with loss of fat planes with PV and superior mesenteric vein (SMV) confluence; C: Carcinoma head of pancreas with loss of fat planes with SMV-PV confluence and dilated common bile duct (\*); D: Neuroendoscrine tumor of head of pancreas with dilated pancreatic duct (#) and adjacent portal vein (^).

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**Figure 2 Endoscopic ultrasound guided of celiac plexus neurolysis, fine needle aspiration and elastography.** A: Fine needle aspiration of mass on head of pancreas with loss of plane with superior mesenteric vein; B: Celiac plexus neurolysis with needle positioned above celiac axis (\*); C: Elastography appearance of carcinoma head of pancreas.

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**Figure 3 Endoscopic ultrasound guided hepatocgstrostomy, radio frequency ablation, biliary drainage and elastography.** A:Endoscopic ultrasound (EUS) guided hepaticogastrostomy with self expanding metallic stent (SEMS) placement; B: EUS guided radio frequency ablation; C: EUS guided CBD puncture and guide wire placement; D, E: Inflammatory pancreatic head mass with sludge ball in CBD (D) and € shows inflammatory pancreatic head mass with mixed signal on elastography.